people very uncomfortable. There are numerous co-morbidities that are part of the allergic condition that are really not amenable to self-treatment and self-diagnosis, and I firmly believe that by taking prescriptions and putting them over-the-counter we will have an increased incidence of those various co-morbidities.

Allergies do not get the respect that they deserve either. As we mentioned, with the number of patients who have allergic rhinitis and the increased incidence of allergic rhinitis we are seeing an epidemic of this disease and its co-morbidities. There is a tendency to trivialize the disease as well. Physicians and other healthcare providers do not get much training in allergic disease. I am a Board certified allergist. In medical school I had one hour of training in allergies. Fortunately, as I proceeded in my specialty we got more training. Most doctors don't even look in the nose, and most patients are extremely confused by the many over-the-counter choices out there. Allergies don't get respect -- "big deal," I hear that all the time. What is so important about a runny nose? And the media doesn't help by portraying allergy sufferers as

wimps. Yet, it is clear that allergies cause millions of days of lost school, lost work and extreme amount of morbidity. As I said before, the mortality isn't due to the runny nose but it is due to the co-morbidities, especially bronchial asthma.

Allergy sufferers have co-morbidities -- asthma, sinusitis, otitis media, urticaria. These co-morbidities, I believe, are increasing in incidence and I think part of this problem -- and we need more data, as you heard earlier -- part of the reason for the increase in incidence in these co-morbidities I think is due to self-medication and lack of physician input into diagnosing and treating these diseases. We have to stop trivializing allergies and start treating them more effectively.

The first stop for most allergy sufferers is the corner drugstore and there is a potpourri of choices, not just the over-the-counter antihistamines but the over-the-counter decongestants, and nasal sprays that are prone to abuse, and the herbal products. It is a mess out there. You almost need some form of medical training to take medicines properly and, believe me, most of the patients I see in my practice are

not taking the medicines properly.

It is clear that many patients who have allergies take just over-the-counter medicines. Forty percent of allergy sufferers take over-the-counter medicines only, and with the complications of inflammation we are seeing, we are seeing an increased incidence of the various co-morbidities.

Another interesting statistic, although 20-30 percent of the population has some form of allergic disease, upwards of 75 percent think they have some form of allergic disease and often self-medicate and often incorrectly. The doctor-patient relationship is crucial for the diagnosis and treatment of allergies. I strongly disagree with the Blue Cross/Blue Shield people who say that you can self-diagnose and then self-treat allergic disease. This is simply not true, and I believe has led to the inflammatory cascade where there are more co-morbidities and complications. I strongly object to the FDA's comments that, quote, allergic rhinitis and related conditions are generally amenable to self-diagnosis and self-treatment. This is plain wrong. It is bad healthcare philosophy. It is bad medicine.

Finally, I ask my patients in my office a little bit about this conversion. Well, first I had a near riot because they were very upset about it and, in very unscientific survey, I asked a hundred consecutive patients what it would do to them. Well, 98 of then were extremely upset and, yes, it would affect them in their pocketbook but, more importantly, it would affect them in their quality of life if they don't have ready access to these medications. They couldn't afford these important medications for treating their allergies if they weren't covered by a prescription plan, and they simply can't afford not to take them. Thank you.

DR. BRASS: Thank you very much. We will next hear from Dr. Emanuel.

DR. EMANUEL: Thank you, Dr. Brass, Dr. Kelly, members of the FDA. I thank you for the opportunity to present my views as a practicing ear, nose and throat allergist.

My name is Ivor Emanuel. I am a practicing ear, nose and throat specialist and allergist in San Francisco. I am a Clinical Assistant Professor in the Department of Otolaryngology at the University of California, San

Francisco, and my affiliations also include the University of California Teaching Hospitals. In addition, I am a fellow and past president of the American Academy of Otolaryngic Allergy and president-elect of the American In Vitro Immunology Society, and I am a member of the American College of Allergy, Asthma and Immunology.

I have been a consultant and have spoken a number of times on behalf of all three companies today, and my participation at this meeting is supported by Pharmacia Diagnostics.

While many issues have been and will be highlighted by numerous groups prior to and during the course of this meeting, perhaps one of the most essential is the importance of an appropriate and accurate diagnosis of allergy prior to the use of second-generation antihistamines. The three second-generation antihistamines under consideration today have been used safely by millions of people. There is no question that they are effective in managing allergy. It is equally clear that when these drugs are inappropriately used they are of no benefit to the many millions of Americans who suffer from non-allergic conditions.

Whether prescribed by physicians or not,

without an accurate diagnosis many of these patients will be denied access to other therapies or approaches that could relieve their suffering. Therefore, my comments today do not directly relate to whether or not effects of fexofenadine, loratadine or cetirizine should be switched from prescription to over-the-counter status but, rather, to the crucial issue of establishing a correct diagnosis prior to their use.

The need for this correct diagnosis prior to the use of antihistamines is highlighted by the results of a recent study at Ohio State University colleagues which found that only 35 percent of patients prescribed a non-sedating antihistamine for allergy symptoms by a primary care physician were actually allergic. These findings demonstrate that a history and physical examination alone is not always sufficient to distinguish between respiratory and ocular allergic disease and symptoms caused by other underlying causes. I suspect that consumer self-diagnosis would be associated with a similar low level of accuracy.

What may not be apparent today is the ease with which an allergy diagnosis can be made with currently available serological diagnostic tests,

the ability of family physicians to order them easily and cost effectively, and the impact these tests can have in directing the patients and consumers to the appropriate prescription and/or over-the-counter options. The use of these tests have been endorsed by the American Academy of Allergy, Asthma and Immunology, the American Academy of Otolaryngic Allergy and the American Academy of Otolaryngology Head and Neck Surgery.

Today, specific IgE blood tests are available for a diverse range of allergens and allow for the accurate diagnosis of both indoor allergens such as dust mites, cats, dogs and common molds responsible for perennial symptoms, as well as outdoor allergens such as pollens and certain molds related to seasonal symptoms.

In the past, physicians have been reluctant to use specific IgE tests due to concerns regarding accuracy and reliability. The introduction of the next generation tests, such as the specific IgE test which exhibits outstanding performance characteristics, can be used with confidence in identifying causative agents in individuals with allergic disease. In addition, this test is the only specific IgE test to receive

FDA quantitation clearance for not only can it demonstrate with accuracy if patients are allergic, but it can also determine the extent to which that patient is allergic. These features, along with the improvements in laboratory facilities, have greatly increased the value and availability of specific IgE testing and have allowed physicians to undertake allergy diagnoses and, therefore, appropriate treatment in their patient populations.

In summary, a positive allergy result from a specific IgE test, such as the ImmunoCap makes it possible to recommend appropriate avoidance measures for indoor allergies maybe not even, therefore, requiring an antihistamine, to use a preventive medication for seasonal outdoor allergies, and rescue medicines for use as needed with symptom breakthrough. Greater utilization of these assays can enhance diagnostic specificity, improve outcomes inn patients with upper respiratory and ocular allergies, and avoid inappropriate use of antihistamines when they are not needed.

I am hopeful that your deliberations today regarding the appropriateness of second-generation antihistamines for over-the-counter status will

include a discussion of the importance of establishing an appropriate and correct diagnosis prior to their use. Thank you very much.

DR. BRASS: Thank you. Our next speaker is Dr. Hussar.

DR. HUSSAR: Thank you for this opportunity to participate. My name is Daniel Hussar. I am a pharmacist and I am on the faculty at the Philadelphia College of Pharmacy at the University of Sciences in Philadelphia. I have reviewed the guidelines relative to conflict of interest. I have spoken in programs that have been sponsored by each of the three companies who are marketing the products we are considering today. I declare that I have no conflict of interest. Indeed, the position I am taking with regard to these products is different from the one that the companies are advocating.

Six hundred deaths and 47,000 injuries each year. These are the estimates of the deaths and injuries occurring each year in the United States as a consequence of motor vehicle accidents that have been attributed or related to the use of nonprescription antihistamines, the antihistamines that cause sedation and other central nervous

system effects. It is well-known and, as has been previously mentioned this morning, these antihistamines such as diphenhydramine and chlorpheniramine cause sedation. Fexofenadine and loratadine are not likely to cause sedation and they are often designated as non-sedating antihistamines. I recognize that this hearing is also addressing the status of cetirizine, an agent that is considered to be a low-sedating antihistamine. Although I can support nonprescription status for cetirizine, my comments are limited to fexofenadine and loratadine because I do not want a debate about the safety of cetirizine to delay a decision relative to the switch to OTC status for fexofenadine and loratadine.

The safety of fexofenadine and loratadine have been thoroughly evaluated. In some studies dosages far above the usual recommended therapeutic dose have been utilized for the reason of demonstrating that these two drugs are not likely to cause the cardiovascular type problems that resulted in the withdrawal of terfenadine and astemizole from the market. I consider the issue that we are addressing today to be a very serious

public safety issue. Many individuals who experience allergy and/or cold symptoms self-treat their conditions with a nonprescription product without visiting a physician. Even though I concur with the importance of effective diagnosis, that situation is not going to change. Many consumers are purchasing these medications without a prescription.

Many of the deaths and injuries mentioned earlier could be avoided if these individuals could use products containing the antihistamines that are associated with the least risk instead of those that cause sedation. Products containing fexofenadine and loratadine are available without a prescription in certain other countries, including Canada. I am not aware of any significant problems that have been associated with their OTC use in those other countries.

During the last several years there has been unprecedented publicity regarding medical errors, drug-related problems, and the safety of medications. Fortunately, there is a course of action that will reduce the risk of death and injuries resulting from antihistamine-related accidents, and that is to transfer fexofenadine and

loratadine from prescription only to nonprescription status.

Unlike most, if not all, previous decisions to switch medications from prescription only to nonprescription status, I would contend that the issue we are addressing now has life or death implications for some individuals. This was not the case, for example, when the histamine H-2 receptor antagonists were switched to nonprescription status.

The need to take action, in my opinion, is urgent. In my opinion, we do not need more studies. In my opinion, we do not need to await the appointment of a new FDA commissioner to take this action. Appropriate labeling for nonprescription use can be quickly developed. There have already been suggestions mentioned. We already have available resources that would permit the rapid development of appropriate labeling through which these agents could be used effective and safely.

I strongly urge these committees and the Food and Drug Administration to take immediate action that will permit the nonprescription availability of fexofenadine and loratadine without

a prescription. I recognize that have some suggested that FDA does not have the authority to transfer medications to nonprescription status if the manufacturers do not wish to do so. I would raise the question if the FDA does not have that authority, to whom can consumers turn when there are questions regarding the safety of the medications that we are using?

I think that there are many additional implications. If, for some reason, there is a determination or a question that the FDA does not have the authority, I think legislative action must be pursued that would provide FDA with that authority, and to also consider legislation that would put these specific agents in the OTC marketplace. If legislation cannot be accomplished at the federal level on a timely basis, I would anticipate there would be action at the various state levels in the interest of public safety. I don't think these steps are necessary. I feel the FDA has that authority. I would urge the committees and the FDA to take this action as quickly as possible. Thank you for the opportunity to participate. I appreciate your consideration of these comments.

DR. BRASS: Thank you. Our next speaker will be Dr. Cutler. If Dr. Cutler is not here we will move on to Dr. Brocato. I apologize for any mispronunciations. I should have said that at the beginning.

DR. BROCATO: You did very well.

DR. BRASS: Thank you.

DR. BROCATO: I am Dr. Frank Brocato. I am not a clinician. I want to make that statement right up front; I have a doctorate in another field. I am representing a coalition. I am not a consultant. I am the president/CEO of an employer coalition in Tampa, Florida, and I am here to address some of these issues from a consumer employer perspective, if you will.

I would like to address the issues of conflict of interest. I own no stock in any of the companies. The coalition paid my way here, and I think the last item is we have, as a non-profit coalition, at different times received some unrestricted grants from pharmaceutical and other companies along with our employers, and they were unrestricted and all of the decisions were made executively by the employers themselves and not by any of the grantors. With that, I will begin.

The Coalition of Employers really looks at value, not just cost. We really are concerned about cost, quality and customer satisfaction. We currently have some major concerns over the issue being evaluated today in terms of a lack of assurance, as well as a concern on the impact from a move from prescription to OTC in regard to medical management of the patients with allergy and asthma that it will not to us -- this is our lack of assurance that it will not yield necessarily the affordability from the patient perspective we are looking for, nor will it yield the proper clinical diagnosis or even the selection of appropriate drug by that particular patient, which is of concern for those who have chronic allergy and asthma particularly.

We did a two-year study and in that two-year study we surveyed 23,000 employee households throughout Tampa Bay. I would like to share some of the results very quickly. There are four areas of benefits that the employers established up front for health care -- faster recovery from illness, improved quality of life, increased functional status which was the preponderance of the survey, and it showed us that

the difference between absenteeism, which everybody has quoted, and impairment by the disease or therapy at the workplace there was a significant difference. In fact, of the 17 diseases we looked at, the impairment at work was 7.5 times greater than absenteeism.

On top of that, when you speak of allergy there was a 32 times greater impairment in the workplace than absenteeism, which is significant to the employer given age and work force and global competition.

On top of that, 26 percent of all those responding were diagnosed by a physician to have allergy. Only 5 percent self-diagnosed themselves. Given that disparity, we have a concern of trying to shift that 26 percent over.

The other is that allergy between prevalence and the cost a loss of days at work times 15 dollars an hour wound up being the highest potential savings of any of the diseases we looked at in the workplace per 1000 employees per year.

The difference between sedative and non-sedative medications was also looked at. We found that in the non-sedative medications the productivity was an average of 600 work days per

1000 per year, which is significant to the employer when we are talking about productivity in the workplace and we are talking about the overall health and safety of the employee. And, that is important to us as employers.

I guess in conclusion I would like to just say that the employers of our coalition, along with 11 of the coalitions throughout the southeast, like ourselves, are looking at the optimal medical and pharmaceutical management of allergy and asthma patients, particularly our employees that we are paying to do a job. We want them to be functional when they are at work; have high productivity and not impact their co-workers because of the burden of the disease and/or the therapy that is currently being prescribed, and this is an issue to us.

I appreciate so much your time and allowing this consumer advocate to come up and present to you. Thank you.

DR. BRASS: Thank you. Next we will hear from Mr. Cloutier.

MR. CLOUTIER: Thank you, Dr. Kelly and members of the committee. My name is Mark Cloutier. I am the policy director of RxHealthValue, which is a coalition of consumer

groups, labor union, healthcare providers, employers, health plans, insurers, pharmacy benefit managers and research institutions, whose mission it is to improve Americans' access to health improving drugs.

RxHealthValue supports WellPoint's bringing this petition before the FDA and the FDA acting in a timely manner. As a general policy, RxHealthValue supports conversion of prescription drugs to OTC in those cases where the medication has low side effect profiles; the condition is easily recognizable by the patient and treated with the OTC product; the use of the product or the medical condition do not require ongoing medical management such as diagnostic procedures, laboratory tests or assessments requiring the technical expertise of a physician; the benefit-risk ratio is of net benefit to the patient; there is a low potential for misuse and abuse; that adequate warnings against inappropriate use or unsafe use can be written; and the labeling is understandable at a reasonable reading level.

The lack of adverse events captured in post-marketing surveillance data in the United States confirms the comparative safety profile of

second-generation antihistamines. Moreover, the experience in Canada, Australia and New Zealand provides evidence of years of appropriate understanding and use of these second-generation antihistamines as over-the-counter products based on labeling offered by the manufacturers. We recommend that the FDA consider reviewing the post-marketing surveillance from these nations and understand that it is not in your purview actually to do that by regulation.

While the advisory committee does not have economic review criteria, there have been extensive comments made by the petitioner, pharmaceutical company representatives, committee members and selected public speakers. Frankly, I am a little concerned about how that is confounding the primary criteria of safety, and recommend that we turn back to those criteria.

Having said that, RxHealthValue acknowledges the potential issues raised in shifting payment arrangements, particularly because we are a consumer and labor union and employer-oriented coalition and we are preparing to respond in a comment to be submitted to the docket.

With regard to conflict of interest

questions, we do not receive any pharmaceutical company money. We are prevented from doing that by our by-laws. We have not been a reviewer of any of the products. We have not been involved in research on any of the products. We do have insurers in our coalition of which Blue Cross/Blue Shield Association is a member. WellPoint, as a plan, is not a member of our coalition. I think that satisfies the conflict of interest questions.

Thank you for allowing us to comment.

DR. BRASS: Thank you very much. We will next hear from Dr. Parker.

DR. PARKER: Good morning and thank you for the opportunity to be here. My name is Michael Parker. I am a practicing physician specializing in otolaryngology head and neck surgery, and I practice in Syracuse, New York. I am on the clinical faculty there at Syracuse. And, I am here representing the American Academy of Otolaryngic Allergy, the AAOA, which is a specialty medical organization. It has about 2200 physicians who treat ear, nose and throat allergies and other upper respiratory tract disorders. The AAOA has in the past received unrestricted educational grants from all three of the manufacturers in question

today.

Additionally, as a physician, I participate as preferred provider with Blue Cross/Blue Shield. So, I get to experience both ends of the conflict here. My experience as a physician, as well as a consultant to Aventis and Schering, I think allows me to have a unique perspective here and, hopefully, a balanced viewpoint.

While representing the AAOA, I am here advocating for the patient's interest. On their behalf, I strongly oppose the proposed shift of second-generation antihistamines from their current status as prescription medications to an OTC status.

The Food and Drug Administration is also in the business of advocating for and protecting patients. It is apparent to the membership of the AAOA that a change in the status of second-generation antihistamines to OTC status would be conflicting with one of the underlying doctrines of both organizations -- to place the patient's interest first.

As physicians with expertise in managing allergic disease, we feel it is critical to

continue to have physicians play an integral role in the diagnostic and therapeutic decision-making process of the symptoms of allergies. The differential diagnoses for nasal congestion and a runny nose are widespread -- from allergic disease to bacterial infections to malignant tumors. It is important to define the cause of the symptoms before proceeding with prescribing and therapy.

In medicine there are abundant situations in which it is necessary to protect the well-meaning patient. the relief-motivated patient from himself. Patient self-diagnosis is not always a simple process, and the allergic disease is no exception. By asking the patient to define and treat their nasal congestion or runny nose you are asking the patient to differentiate allergic disease from other disease states. The ability to differentiate diseases is a skill that physicians develop after years of education and experience. By allowing these second-generation antihistamines to be dispensed over-the-counter more and more patients will attempt, or worse, be expected to self-diagnose and treat their symptoms, allergic or not.

While antihistamines may easily treat some

patients who suffer from simple allergic disease, there are a number of variables that must be considered to successfully manage most patients with allergies. Second-generation antihistamines are clearly superior to OTC preparations with respect to the reduced side effects. This fact actually contributes to an increase in the potential for over-use. Self-diagnosed patients who treat themselves with second-generation antihistamines inappropriately will find it easier to remain on the drug. For example, if a patient did have an upper respiratory viral infection, a condition which typically resolves spontaneously, and self-treats with this class of drugs, the patient would perceive success with the drug and continue taking the drug erroneously. A similar situation already exists with another class of OTC preparation and, indeed, results in a disease state from overuse. Rhinitis medicamentosa is a well-documented condition that we see often resulting from patient self-diagnosing and prolonged use of topical nasal decongestants.

Utilization of second-generation antihistamines by patients without physician evaluation may also lead to problems of masking

diseases or delaying the diagnosis of more serious conditions. Diseases such as acute sinusitis, pathologic obstruction, nasal polyposis, chronic sinusitis, otitis media or asthma can all exist with or without or with an allergic component. Defining which disease is contributing to which symptom is often difficult for a physician lacking specific expertise in this area. As such, patients self-diagnosing and prescribing antihistamines can only delay and confuse proper diagnostic and medical or surgical management.

Leaving second-generation antihistamines as prescription medications will assure that allergic disease will be properly diagnosed and managed by physicians. Maintaining the current status will assure that more serious conditions will not be undiagnosed, and that patients will not be medicated inappropriately for diseases they do not have.

I would suggest to you that keeping the physician in the loop is in the patients' best interest. An appropriately trained healthcare professional is best able to assure that the symptoms of simple allergies are not those of a more serious disease, that simple problems do not

become serious problems, and that curable diseases do not become incurable, for example, a runny nose, proved by an over-the-counter second-generation antihistamine is not allowed to mask a potentially deadly malignant nasal mass.

In exercising its responsibility to protect the patient, the FDA must recognize that it is in the patient's best interest to preserve the status of these second-generation antihistamines as prescription medications. Thank you.

DR. BRASS: Thank you. We will now hear from Dr. Quel.

DR. QUEL: I am Dr. Quel, executive director of the Spanish-American Allergy Asthma Immunology Association. My income is coming from private practice. I am a Board certified allergist. My presentation and related expenses have not been, and will not be covered by a sponsor. I have not been an investigator for the three current second-generation antihistamines, Aventis, Pfizer or Schering Plough. I am not aware of any other way in which I may be in conflict. I will start my presentation.

I have served as a consumer representative, as well as a member of the

Allergenic Products Advisory Committee and, therefore, have closely followed FDA regulations and regulation changes. The decision regarding these medications is an extremely important one because its outcome will have a ripple effect on the health care of our society.

In order to decide if a drug is a candidate for an OTC switch numerous issues involving safety must be considered. One of the switch principles asks if the candidate has been used for a sufficiently long time on the Rx market to enable a full characterization of its safety profile.

At the time of Blue Cross' original petition, fexofenadine (Allegra) was prescribed at a dose of 60 mg twice daily. Last year it was released on the market with a dose of 180 mg once a day. Insufficient time has passed to permit an accurate characterization of the safety profile on this recent dosage.

A prescription formula for loratadine (Claritin) for children aged 2-5 was approved only 5 months ago. Should the adult doses of loratadine be approved for OTC, it is very probable that parents will use the adult doses off label for

their children.

Cetirizine (Zyrtec), due to cross-reactivity and recently released pediatric doses has also had insufficient time for characterization of a safety profile.

It is important to remember nearly a ten-year process passed before it was realized there were cardiac side effects with terfenadine when used with other medications. A similar lapse of time occurred before the same problem was discovered with astemizole. Nor should we forget the recent action taken with PPA.

Another question asked by the switch principle is if the candidate safety profile has been defined at a high dose. This is not the case with the medications in question, and it is definitely not the case with one of the drugs being discussed which was released at a higher dose only one year ago.

The use of antihistamines combined with pseudoephedrine at a high dose of 240 mg in a single tablet form for use on a daily basis should raise serious concerns about switching it to an OTC. Since studies have shown that a majority of OTC drugs are used more than once daily, it is

possible, and perhaps even likely, that the public may use the non-sedating medications more than once daily. Concern must also be focused on special population groups such as the elderly as these drugs require dosing adjustments in patients with renal impairment.

Allergies are more prevalent than ever. In fact, it might be said that we are currently having an allergy epidemic. The important fact to realize is that one form of allergic disease can cause or worsen other symptoms. Recent studies have indicated that up to 80 percent of asthmatics have rhinitis.

It has been acknowledged in several consensus reports that allergic rhinitis is associated with impairment of daily function at home, at work and in school. The use of antihistamines is not a simple solution to a more complex management of an allergic condition and related diseases such as asthma, otitis, sinusitis and urticaria. Mortality due to asthma is on the rise and, therefore, we must recognize the importance of physician guided control of the allergic condition. Careful control of allergic rhinitis will have a direct effect on asthmatic

patients.

The treatment period of seasonal allergic rhinitis has tremendous variations nationwide. Because plants pollinate ten months out of a year in the State of California, the use of these drugs is more frequent and persistent. This factor provides a different perspective to Blue Cross of California's petition and elevates the need for caution.

What is the worldwide experience of the switch candidate? The Blue Cross petition bases its safety evidence on a Canadian adverse drug reaction database that combines data from clinical trials with different methodologies. Further outcome data and review are necessary for proper assessment of safe use without physician supervision. Furthermore, contrary to Blue Cross assumption, the use of non-sedating prescriptions is higher in countries where these medications are prescribed by a physician.

An OTC switch will deprive an indigent population of the use of these drugs. If switched to OTC, approximately ten million patients will not be able to use these drugs. Instead of improving health care, we will be jeopardizing patient

safety. Thank you.

DR. BRASS: Thank you. We will now turn our attention to the FDA presentations addressing the issues before us today, and my understanding is the first presentation will be done by Cazemiro Martin.

FDA Presentation

OTC Considerations

MR. MARTIN: Good morning.

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My name is Cazemiro Martin, and I am from the Division of Over-the-Counter Drug Products at the Food and Drug Administration.

This morning I would like to give you a brief review of the regulatory basis that establishes the conditions under which current OTC antihistamine ingredients are generally recognized as safe and effective and not misbranded.

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In 1951 the Durham-Humphrey Amendment of the Federal Food, Drug and Cosmetic Act was passed. This act formally differentiated between prescription and OTC drug products. It provided that a drug be sold OTC if it is safe and if adequate directions for use can be written which

are readily discernable by a lay person so that a professional's advice is not required for the administration and use of the product.

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The Durham-Humphrey Amendment currently describes two conditions under which a drug is to be dispensed by a prescription. The first condition as described in 503(b)(1)(A) of the Act is because of toxicity or other potentially harmful effects or the method of its use the drug is not safe for use except under the supervision of a licensed practitioner to administer the drug product. Or, as described in 503(b)(1)(B) of the Act, when the drug is limited by approved application to be used under professional supervision or a licensed practitioner.

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A drug can be made available OTC by two regulatory avenues. The first avenue is by way of a new drug application process, or NDA route. By this process a drug product can be marketed OTC as a prescription to OTC switch, or directly OTC under an approved application.

Let me point out that the switch of a prescription drug to OTC requires a review of the

post-marketing safety data and a determination that consumers can adequately use the product in an OTC setting.

The second way a drug can be made available OTC is by the OTC drug monograph process. This process establishes conditions under which OTC drugs are generally recognized as safe and effective, or GRAS/E.

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There are several questions to ask when considering if a drug should be switched from Rx to OTC. These include the condition for which the drug is intended be adequately self-recognized? Can the condition be successfully self-treated? And, is the self-treatment product safe and effective during consumer use?

If the response to these fundamental questions is yes, then the proposed drug product may, indeed, be a likely candidate for OTC availability.

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With regard to an Rx to OTC switch candidate, it is essential that the proposed switch candidate has an acceptable margin of safety based on prior prescription marketing experience. It is

important that the proposed OTC dosages and indications for the drug are relatively safe, and that there is a low misuse potential and minimal abuse potential. In addition, the switch candidate should have a therapeutic window that is reasonably wide enough to ensure an acceptable margin of safety if a higher than recommended dose is taken.

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It is essential that the switch candidate provides an OTC indication that enables the consumer to self-treat and to self-monitor with minimal physician supervision. It must also be determined that the switch candidate can be adequately labeled to allow safe and effective use. Consumers should be able to understand when to use the product, what are the potential benefits and risks, and how to use the product. Finally, the benefits from the OTC switch must clearly outweigh the risks.

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As I mentioned earlier, the second avenue leading to OTC availability is by way of the OTC drug monograph process. Most of the antihistamines currently available OTC are marketed under this process which, again, establishes the conditions

under which OTC drugs are generally recognized as safe and effective.

The OTC drug monograph process essentially involves a four-stage procedure that includes the deliberation of an advisory review panel, followed by the development and subsequent publishing in the Federal Register the following notices, an advanced notice of the proposed rulemaking that includes the advisory panel report, followed by a tentative final monograph, or TFM and, lastly, the publishing of a final monograph.

Let me point out here that public comments are requested in response to the advance notice of the proposed rulemaking and the tentative final monograph. You will find in your background package these publications that specifically relate to the OTC drug review of antihistamine products.

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With regard to the OTC antihistamine ingredients currently available under the OTC drug monograph process, a single advisory review panel was established for the OTC cough, cold, allergy, bronchodilator and antiasthmatic drug products. This panel is referred to as the cough/cold panel.

As part of the OTC drug review process,

the cough/cold panel reviewed data and information submitted to it concerning OTC antihistamine ingredients. Upon completion of its review, the panel prepared a report to the FDA Commissioner. This report outlined the panel's recommendations and proposed monograph conditions under which OTC antihistamine drug products are generally recognized as safe and effective and not misbranded under recommended and suggested conditions of use.

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In the Federal Register of September 9, 1976 the agency published an advance notice of proposed rulemaking to establish a monograph for OTC cough, cold, allergy, bronchodilator and antiasthmatic drug products. The notice also included the cough/cold panel's report concerning OTC antihistamine ingredients. In its report, the panel indicated that antihistamines are effective in suppressing symptoms of allergic rhinitis, such as hay fever, and that OTC antihistamines have a low order of acute and chronic toxicity.

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The panel noted that because first-generation antihistamine active ingredients readily cross the blood-brain barrier, the most

common CNS side effects include sedation and cognitive impairment which are widely recognized as drowsiness. The panel pointed out that anticholinergic side effects are also common with the use of these first-generation antihistamine ingredients.

Such effects include dryness of the mouth and urinary retention. The panel also noted the generally held belief that first-generation antihistamines may reduce the volume and cause thickening of bronchial secretions. Other less common cardiovascular, gastrointestinal and hematological side effects were mentioned in the panel's report to the Commissioner.

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In its report, the panel also recommended dosages, dosing intervals and labeling for OTC antihistamine ingredients. With regard to the labeling of these ingredients, the panel recommended that antihistamines be labeled for temporary relief of symptoms associated with allergic rhinitis and include adequate warnings for the safe and effective use of these products.

Recognizing the potential harm with the use of these products under circumstances in which

alertness is important, the panel proposed that the labeling include cautionary or warning statements that relate to drowsiness, driving or operating machinery, and the use of alcoholic beverages when taking these products.

With regard to the anticholinergic effects, the panel recommended that the labeling include warnings against use of antihistamines if consumers have difficulty in urination due to prostatic hypertrophy or if the consumer has breathing problems such as chronic bronchitis of emphysema, unless directed by a doctor.

[Slide]

After reviewing the comments and the new data submitted in response to the advance notice of proposed rulemaking, the agency published a tentative final monograph, or TFM, in 1985. This document describes the agency's position concerning conditions under which OTC antihistamine drug products are generally recognized as safe and effective. Comments and any new data and information were, indeed, requested in response to this document.

[Slide]

After reviewing additional data and

information and public comments in response to this TFM, the agency published in the Federal Register of 1992 a final monograph for OTC antihistamine drug products. The final rule establishes conditions under which 13 OTC antihistamine ingredients marketed, again, under this OTC monograph process, are generally recognized as safe and effective. The final rule also addresses allergy indications only and provides class labeling for the antihistamine ingredients included in the monograph.

[Slide]

This slide identifies the 13 immediate release antihistamine ingredients in the final rule, in the final monograph. This list, however, does not include extended release OTC antihistamines or other OTC antihistamine ingredients currently marketed under the NDA process.

[Slide]

Those ingredients that are marketed under the NDA or abbreviated NDA process are listed on this particular slide.

[Slide]

There are six ingredients that were not

included in the OTC antihistamine final monograph. The reasons for not including these six ingredients include potential carcinogenicity, lack of adequate and effectiveness data, no safety or effectiveness data submitted, and unresolved questions concerning promethazine's causal role in tardive dyskinesia. I ask you to please keep in mind the reasons that I have mentioned for not including these ingredients in the final monograph as you listen to the next presentation.

[Slide]

As I mentioned previously, the final rule for OTC antihistamine drug products provides class labeling for the safe and effective use of these products. This information will soon appear, as some manufacturers have already done, in the new OTC drug facts labeling format, which is described in Section 201.66 of the Code of Federal Regulations.

[Slide]

This new format will enable consumers to easily find and understand important information included under various headings and subheadings within the drug facts enclosure. You have been given an example of an OTC antihistamine label in

this new drug facts.

The standard labeling format and the labeled use claims are the same for both monograph and NDA approved OTC antihistamines. However, content label may vary to some extent based on ingredient-specific or product-specific data-driven differences. Please note that in this new format the side effects of drowsiness and urinary retention, as well as information concerning when to consult a doctor or a pharmacist before using these products are prominently listed under specific warning headings. Similarly, the directions section will be easier to find and understand in this new format.

[Slide]

In summary, when considering whether or not a drug product should be available OTC, the agency's primary concern is an assessment of the overall margin of safety and effectiveness. Factors that suggest an acceptable margin of safety include minimal toxicity, low potential for harmful effects, low potential for abuse and misuse, and a therapeutic window that is reasonably wide enough to ensure an acceptable margin of safety.

In addition, the consumer must be able to

successfully self-recognize and self-treat the condition for which the drug ingredient is intended. To further ensure an acceptable margin of safety and effectiveness, it must be determined that the drug product can be adequately labeled to ensure safe and effective use. Of equal importance certainly, the benefits of using any OTC drug product should outweigh the risk.

The agency has carefully evaluated the risk inherent in the OTC availability of antihistamines, and has concluded that with appropriate labeling these products can be considered reasonably safe and effective to use in an OTC setting.

Our next speaker will be Dr. Robert Meyer, Director of the Division of Pulmonary and Allergy Drug Products. Dr. Meyer will discuss the clinical and safety perspectives on the citizen petition submitted by Blue Cross of California. Thank you for your time and attention.

Clinical Safety Overview

DR. MEYER: Thank you. As we are getting the slides set up -- I have a fair number of slide to move through so I will do so with some dispatch. I am glad I don't have a long disclosure statement

to make. I can assure you I work neither for a managed care organization nor for a pharmaceutical firm.

[Slide]

As we have just emphasized and as I want to reemphasize here, some of the important considerations for an OTC switch include the ability of a consumer to either self-diagnose and/or self-manage, as well as the safety and the effectiveness of particular drugs used in that setting, in other words, without a learned intermediary.

[Slide]

In many cases where these switches are proposed by sponsors, these considerations may be addressed through actual use studies meant to replicate the OTC setting and/or label comprehension studies, these focusing on issues within the labeling that might be specifically of question for that drug product or indication.

[Slide]

All three of the drugs that are listed in the citizen petition are antihistamines, and though there are other approvals that are part of their labeling they are all approved for allergic

rhinitis. As already pointed out in the previous talk, FDA accepts allergic rhinitis to be an appropriate OTC indication and, furthermore, FDA accepts antihistamines as appropriate for the OTC use.

Back on this bullet, I would point out though that it is not just antihistamines that we have accepted as being appropriate in the OTC setting. These same two committees have met in the past to discuss things like nasal crom, for instance, which has an allergic rhinitis indication. And, as Cazemiro Martin pointed out, we have established appropriate OTC labeling for antihistamine products both under the monograph as well as NDA antihistamines that have been switched to the over-the-counter status.

[Slide]

Therefore, in terms of an actual requirement for such a switch as proposed by the petition, FDA has determined that neither an in-use study nor a labeling comprehension study is strictly necessary for the OTC switch proposed. Because of this, we are also not seeking advice today, although it has come up as a question, about allergic rhinitis as an OTC indication. That is

not the intent of today's meeting, to revisit that decision. Nor are we wanting to focus on the effectiveness of Claritin, Zyrtec or Allegra in the OTC setting. I think we accept that they are effective drugs and since other antihistamines are effective in that setting we accept that these would be as well.

[Slide]

So the focus today will really be on the safety profile that we have with these particular agents, both pre- and post-marketing. In many ways, FDA -- and this was a large working group that had components from the Division of Pulmonary and Allergy Drug Products, the Division of Over-the-Counter Drug Products, as well as the Office of Post-Marketing Risk Assessment -- the FDA performed a safety review of these items in many ways to address the kind of questions that we expect sponsors to address when they propose a switch. Of course, there were other data submitted by the petitioner and available in the literature and elsewhere to also help inform this review.

[Slide]

The elements of the presentation that I am going to give will first focus on the NDA database,

which included standard safety data that you would get for just about any new drug application, specific cardiac safety evaluations that were done for these drugs, as well as issues related to any drug-drug interactions or other metabolic considerations. Also, we will review the post-marketing experience, and this consisted of case review of our adverse event reporting system, or the AERS system -- I will use this acronym frequently throughout the rest of the talk.

In the NDA review we focused on the single ingredient compounds. The combination products in question in the petition contain daily amounts of pseudoephedrine that are within the monograph dosing, although in a controlled release form and, furthermore, there are NDA controlled release antihistamine decongestant combinations available over-the-counter. But because pseudoephedrine does have some known cardiac effects, they may confound the look at safety, particularly the cardiac events, so we focused the NDA review on the single ingredient information. However, in the post-marketing data it is not always possible to separate out from the reports whether the specific report is for a single ingredient product or a

combination product.

[Slide]

I do want to make some caveats here about the safety data. The safety review is not intended to be comparative of the three agents. In fact, we have fairly scant data that would rigorously compare these three agents, and that is not our intent although, because there are three items or three drugs listed in the petition, I will be talking about the experience with the three in close proximity.

We are also not here to really attempt to rigorously compare these products to the OTC antihistamines. I would point out that there was an earlier statement made that we have concluded that, in fact, these drugs are safer than the OTC antihistamines and that is not the intent of the FDA safety review nor was it a conclusion of our safety review. Rather, the safety review is meant to focus on the safety experience with these agents individually and on their own, regardless of the experience of the other OTC available antihistamines.

[Slide]

Furthermore, I want to also point out that

our most definitive safety data in terms of establishing any kind of causality comes from controlled studies within the NDA. Post-marketing data is very useful and, in fact, is clearly a way to signal or to see signals of perhaps some rare events that couldn't be detected in an NDA because an NDA has a limited number of patients exposed, albeit these particular drugs had very reasonable numbers but we know from experience that even very large NDA databases may not fully define the safety profile for very rare events. On the other hand, the post-marketing data can be very, very hard to assess for any degree of causality. Unless it is a clearly distinct signal, it may be very difficult to know whether anything seen in the adverse event database is really causally related to the drug.

In an attempt to at least put some of the signals that we saw in perspective though, an epidemiology evaluation was done but, again, due to the limitations of the data available this is not a definitive look.

[Slide]

So, we are here to talk about the safety experience of three different drugs sold under the brand names of Claritin, Zyrtec and Allegra. The

Claritin original NDA was approved in 1993, and it is currently approved in five different dosage forms, down to age two. I should point out right here, however, that just as earlier Dr. Ganley had said that each of these drugs should be considered separately in further discussions, it is not necessarily the case that all age ranges, all formulations and/or all indications would be proposed or thought of as part of the OTC switch. For instance, the CIU, or chronic idiopathic urticaria, is not a well-established over-the-counter indication.

Cetirizine was approved for marketing in December of 1995, and Allegra in July of 1996, and cetirizine is currently labeled down to age two in two dosage forms, and Allegra down to age six in three dosage forms. As pointed out by the sponsor, we have been working with the sponsor to establish more pediatric data with Allegra.

[Slide]

So, in reviewing the NDA safety data first, I would like to go through the number of patients exposed during the original NDA; the safety experience in the clinical trials, and this will be mainly highlighted in the major experience;

a brief discussion of the cardiac safety data that have been established for that specific moiety; and then touch upon drug interactions.

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Why the focus on the cardiac safety and the drug-drug interactions? Part of this, as you have already heard, arises from the experience with Seldane, or terfenadine, which is the parent compound of fexofenadine. In this particular case, it was the parent compound that had the dire cardiac effects that came out. I would also point out that we knew of those cardiac effects much earlier than the ten years that it took for that drug to be withdrawn from the market. In fact, there was an advisory committee about the adverse effects in 1990, which was about five years after it was originally marketed. But, in any case, the effects for Seldane were malignant arrhythmias occurring in a setting of metabolic inhibition or drug-drug interactions, and there was a similar issue, of course, we astemizole which led to its withdrawal.

[Slide]

In addressing the cardiac safety once the underlying problem was better established, there

are certain sets of studies that are expected or commonly done for workup of the cardiac effects. These include in vitro studies of specific ion channels, including recombinant human channels; in vivo high dose animal studies, as well as clinical data such as high dose studies or drug interaction studies.

[Slide]

First turning to Claritin, and I will go through the NDA database for each drug before turning to the next, there were over 90,000 patients exposed for the original NDA. This is actually a very large database. The adverse event profile seen was quite consistent with an antihistamine given to this population. We had no significant clinical safety signals at the time of the approval of the original NDA.

[Slide]

This table is taken from the labeling, and it is meant to represent the most frequently reported adverse events with Claritin that had some excess in incidence related to placebo, in other words, where there might be some signal of causality.

These events for Claritin included

headache, somnolence, fatigue and dry mouth. I would point out, sine I am going to be showing data in relative close succession here, that you really need to look at specifics of the drug and placebo rate within these tables, and not compare across these tables.

[Slide]

One thing that did come out of the Claritin NDA database is that the somnolence reported, which at the recommended dose was quite comparable to placebo, was dose related and, in fact, was 10-12 percent with the 20 mg daily dose and 12-13 percent with the 40 mg daily dose. Pediatric studies done have shown a similar adverse event profile, again, for what would be expected for an antihistamine given to an allergic population. Some other terms that showed up in excess to placebo at a fairly low incidence included things like nervousness, hyperkinesia, wheezing and abdominal pain. But, again, there were no significant safety concerns at the time of the approval of the original NDA or the pediatric indications.

[Slide]

For the Claritin cardiac safety, the in

vitro testing, both through ion channel testing and myocardial cells, was negative. There were no QT or repolarization effects documented in animal studies. Furthermore, with high dose clinical studies at up to 16 times the currently recommended dose, there is no significant cardiac effect seen in the clinical trials, including any measurement of perturbation of the cardiac repolarization or QTc on the cardiogram. There was a QTc effects that were felt to predict Seldane propensity for leading to malignant arrhythmias when co-administered with drugs that inhibited its metabolism.

[Slide]

For the metabolic considerations, the drug-drug interactions with Claritin, it is largely metabolized by the cytochrome P3A4 as well as the 2D6 pathways. In fact, drug interaction studies were done with erythromycin, dimetidine and ketoconazole, and they showed some increase in loratadine and its major metabolite desloratadine exposure when co-administered with these drugs but certainly not to the degree that was seen with Seldane and its parent compound of terfenadine. Furthermore, there was no apparent clinically

significant impact of this interaction, in other words, no effect on the cardiogram.

Renal and hepatic insufficiency decreased clearance with loratadine and there are some dosing recommends for dosage adjustments related to patients with these conditions.

[Slide]

For the Zyrtec NDA database, I would just point out that Zyrtec is an active metabolite of hydroxyzine which is a prescription antihistamine, and the safety profile of that may, in fact, offer some information about the safety of Zyrtec itself. But for the ingredient and compound cetirizine in question, we had over 3900 patients treated during the clinical trials with the original NDA. Again, the adverse event profile was what might have been expected with an antihistamine given to allergic patients.

[Slide]

This again is a table extracted from the package insert that shows the major adverse events that were reported, or the most frequent adverse events, I should say, that were reported during the clinical trials with cetirizine, with somnolence being at 13.7 percent versus a placebo rate here of

6.3 percent. The other common adverse events cited were fatigue, dry mouth, pharyngitis and dizziness.

[Slide]

Somnolence was dose-related. There were actually two doses recommended in the Zyrtec package insert, both the 5 mg and the 10 mg dose, and actually the rate for somnolence was 11 percent for the 5 mg and 14 percent for the 10 mg and, again, the placebo rate was 6 percent as shown on the last slide.

Again just highlighting some of the experience in children for events that were reported higher than placebo that were not necessarily as high up on the list in adults, we had things like abdominal pain, diarrhea and vomiting -- so, some low-level GI effects were reported. Interestingly, in children the somnolence was reported only in 1.9 percent of the children at 5 mg, 4.2 percent at the 10 mg. Here the placebo rate was about 1.3 percent. Again, no significant safety signals arose from the original NDA.

[Slide]

The Zyrtec cardiac safety was again quite reassuring in that in vitro testing revealed no

significant effects are relevant concentrations. There were no significant QT or repolarization effects seen in whole animals. There were no significant cardiac adverse events seen in the clinical trials, including trials up to six times the recommended daily dose.

I would point out, however, that one safety exposure study done did show what appeared to be an increase in QTc, that interval of the electrocardiogram, using a specific formula for correcting for heart rate called Bazett's correction. I think it is fairly well appreciated that Bazett's, for drugs that can increase the heart rate, tends to exaggerate this number, but this was placed in the labeling for Zyrtec just because it was information we had and we felt it was important to be conservative in relaying that information. However, I think all these data taken together would suggest that Zyrtec really does not have a potential to significantly impact on the cardiac repolarization.

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For metabolic considerations for Zyrtec, it is renally excreted, largely in an unchanged state. Therefore, there are not many or any

significant drug-drug interactions. Renal impairment, not surprisingly, does cause a modest decrease in clearance, so a modest increase in exposure. And, hepatic impairment causes a small effect on clearance as well. Again, there are some dosage recommendations in the labeling.

[Slide]

Allegra, fexofenadine, as I pointed out earlier is the active metabolite of terfenadine but it does not have the apparent QT properties of the parent compound, as I will get to in a minute. We had over 2300 patients exposed to Allegra in the original NDA database.

[Slide]

Here is another table extracted from the package insert, showing the top reported adverse events and their relationship to placebo. These are all events that occurred in excess to placebo, and included such reports as viral infections, nausea, dysmenorrhea, drowsiness, dyspepsia and fatigue.

[Slide]

Except at very high doses, the evidence in the NDA was that there did not seem to be a clear dose relationship to any reports of somnolence with

fexofenadine. The adverse event profile from the pediatric studies down to age six, in addition to what might be expected for this class of agents given for this indication, included headaches, accidental injuries, cough, fever, pain, otitis media and upper respiratory infections. Again, no significant safety signals at the time of the NDA approval.

[Slide]

Not surprisingly, Allegra, fexofenadine, underwent a very full safety evaluation and, again, it was very reassuring. In vitro testing of ion channels and isolated myocytes showed no evidence of repolarization effects. Whole animal studies showed no effects even at high levels of exposure, and there were no significant cardiac events reported in clinical trials either at recommended doses or, in fact, very high doses compared to what is recommended.

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The other feature that makes fexofenadine very distinct from its parent terfenadine is that it has very little in the way of metabolic considerations. It is minimally metabolized itself, although drug interaction studies showed a

small increase in serum levels or levels of exposure when concomitantly administered with drugs like ketoconazole. It wasn't well understood at the time and later it appears to perhaps be related to the intestinal absorption through organic ion transported proteins and P glycoprotein. But there is no evidence of important changes in metabolism in special populations nor important drug-drug interactions.

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Therefore, to summarize the data, not surprisingly considering these are approved compounds, the FDA felt that all three of these drugs showed an acceptable safety profile in their various NDAs. The workup for cardiac effects was reassuring. Although Claritin does have some drug-drug interactions mentioned in the label and known drug-drug interactions, these do not have any apparent clinical consequence and, again, are not in the same kind of order of magnitude as those seen with terfenadine.

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Are there some additional caveats before turning to the post-marketing experience? Clearly, the duration of marketing will affect the total

number of reports even if there is no causality to any of the reports. The longer the drug is out there, the longer it has to receive reports.

The extent of use, similarly, will affect the total number of reports that come in. Finally, heightened sensitivities and other temporal trends may affect the number of reports for any specific drug. I mention this partly because Claritin was approved earlier on than the other drugs and was marketed at a time when there was really a heightened sensitivity to some of the cardiac effects.

[Slide]

In working on these issues in response to the citizen's petition, the FDA had originally done some of this work in April of 2000 but we have updated it for looks at serious events that have been reported in the last year.

Overall, this assessment shows that all three drugs have a good post-marketing safety profile, though there are a few signals seen in the adverse event reporting. However, if we were not here discussing the OTC switch, I would like to emphasize that none of the issues we found in our review would warrant reconsideration for overall

approval or marketing.

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Again, we are not going to rigorously compare to the OTC antihistamines but we did, in our safety review, attempt to look at the experience with the OTC antihistamines. Partly because of the difference in the reporting systems or things like monograph antihistamines, because of the different temporal trends, the length of time these products had been marketed, it is really not amenable, the data are not amenable to a rigorous comparison to what we have for the prescription products in question today. However, it is clear that central nervous system events, particularly sedation and altered motor performance, are quite common as are anticholinergic effects. Rare cases of seizures, liver failure or serious cardiac events and other rare events have been noted both for specific drugs as well as generally in the literature.

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I would point out quickly here that the over-the-counter antihistamines actually carry some caveat about their use in airway disease due to their bronchial secretion drying properties. In

fact, some of the labeling for the drugs in question today have had that specifically removed because of the safety data that suggests that they are not problematic when given to asthmatic patients.

[Slide]

We have over 4081 spontaneous adverse events in the database that we looked at for all loratadine products. Again, I would emphasize that this would include some pseudoephedrine products. The top ten adverse event terms in terms of frequency of reports are drug ineffective, drug interactions, headache, palpitations, dizziness, tachycardia, insomnia, sedation, dermatitis and nervousness. Again, I want to emphasize that these would include some pseudoephedrine products. So, some of these items on here are known properties of pseudoephedrine and may confound the consideration of these specific events.

[Slide]

Because of the question about cardiac effects with the newer generation antihistamines, we did review the serious cardiac events for Claritin in depth. Out of all the cases reported, there were actually 86 cases that were looked at

because of at least some plausibility that they could be related to drug exposure. This is not to infer causality, but there were some cases that clearly could not have been due to drug exposure.

Patients in these reports were ranging in age from about 2 years old to 87 years, although about 40 percent of these patients were less than 50. The large majority of these cases occurred in a setting of confounding factors.

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There are some hepatic terms in the approved Claritin labeling in terms of adverse events for which there has been some notice either in clinical trials and/or in post-marketing experience, again, without clear causality. But that led us to at least look at the hepatic experience with Claritin. In fact, there are five cases of hepatic failure in the adverse event reporting system for Claritin. However, three of these five had confounding factors such as foreign travel or other suspect drugs that might cause liver injury. That left about two of the five that were otherwise unexplained but, again, without any clear causality.

I should also point out that for all these

events that I am focusing in on here, there is a known background rate in the population. So, any widely used drug might be expected at some point, even if it did not cause the event, to be taken in patients who experienced the event.

[Slide]

Post-marketing experience for Zyrtec -- we had about 3000 spontaneous adverse event reports in the database, and the most commonly reported were drug ineffective, sedation, thrombocytopenia, urticaria, dermatitis, pruritus, drug interaction, asthenia, headache and hypersensitivity. There is no currently marketed pseudoephedrine formulation for Zyrtec, I should point out, so these are all single ingredient.

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The thrombocytopenia stuck out to us in that list so we did further assessment of that. In fact, there was one case without any clear causality reported in the NDA database. Out of the 170 cases in the adverse event reporting system database, all but 11 cases were not reasonably or plausibly linked. So, there didn't even appear to be a good possibility that we could link those to possible Zyrtec exposure. Of these 11 cases, a

relationship could not be excluded but neither, would I add, could a relationship be established. I would say that the possibility of thrombocytopenia is listed under post-marketing events in the Zyrtec labeling.

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Seizures which, at least in part, have been implicated as occurring in OTC antihistamines, were reported in 64 separate cases for Zyrtec and 38 of these were reviewed in depth. Of those 38, 5 were not apparent seizure events although they probably do fit into the category of a significant CNS effect. Patients who experienced these seizures were in the 3-79 years age range. Twenty-one of these were new onset; 12 were preexisting seizure.

I am sounding a little bit like a broken record, although we couldn't exclude a link between the possibility of these seizures, either new onset or worsening seizures, being linked to Zyrtec, there is also no data to establish that link either.

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For serious cardiac events with Zyrtec we had 37 cases that were reviewed in depth, patients

ranging in age from 3-80 years. About half of these were under the age of 50. Again, as sort of a recurring theme here, the majority of these cases had confounding features, either preexisting disease, other drugs that might cause the particular cardiac event, or other features that would confound trying to establish causality.

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For fexofenadine, the most recently marketed of these three drugs, we had about 1768 spontaneous adverse events reported. Again, the most common top ten items are here -- drug ineffective, nausea, dizziness, dermatitis, headache, sedation, insomnia, palpitations, diarrhea and dyspnea. And, fexofenadine is available in a combination product although there was a gap in the marketing of the two to some degree.

I want to point out here, although I am not going to go into any details about it, the FDA team did also look at the safety experience for terfenadine because it seemed to us that one of the major pathways of action for terfenadine was, in fact, its metabolism to fexofenadine, its active metabolite. And, other than the cardiac safety

issue, we thought that in many ways, since the exposure levels were comparable of the two drugs, that the terfenadine experience would also inform the fexofenadine review. In fact, it largely echoed the Allegra experience except for the fact that the cardiac profile is obviously very different.

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For the serious cardiac events with Allegra there were 39 cases reviewed for patients ranging in age from 15-89 years. Again, the most serious cases had a prior history of cardiac disease or concomitant drugs that could otherwise lead to serious cardiac events.

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Also, we had some reports of seizures st fexofenadine. We had 17 cases that we reviewed in depth because of at least some possibility of a causal link. The patients in these reports were from 22-80 years old. Nine patients had no previous history of seizure; 10 patients were on drugs known to cause seizures; 8 had apparent positive dechallenge, in other words, they had an isolated event; and 1 possible rechallenge, although I would point out that the apparent event

on restarting fexofenadine was unwitnessed so it is not entirely clear whether it was a seizure.

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So to summarize the post-marketing safety experience or review for these drugs, we do have some signals that arise in a loot at the AERS database. After careful review, each drug has some cases of cardiac events and seizures that cannot be otherwise explained, and all these events occur with some background rate in the general population, as I earlier pointed out.

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In part then, to try to address this issue to see whether we could put these reports into some perspective, the epidemiology staff within the Office of Post-Marketing Drug Risk Assessment estimated background reporting rates for these three drugs versus expected background incidences in the general healthy population. The events examined were serious cardiac events, seizures and, in the case of loratadine, hepatotoxicity.

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The background incidence rates were estimated for comparison purposes, and came from estimates in a young population, 15 to the mid-40s,

who were otherwise healthy. So, these were a low risk population that the incident rate was drawn from. I would point out, however, that the drug experience comes from a mixed risk population. The denominator used was inferred from actual use data.

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In terms of the numbers that we are talking about here, serious cardiac events of the kind that were the focus of our inquiry, occurred in about 44 per million person-years -- this is an estimate -- in the population, the young, healthy population. Seizures occurred at a rate of about 90 per million person-years, and hepatic failure, not surprisingly, is lower than those, at about 1 to perhaps as high as 2.3 per million person-years. That is the background rate for idiopathic hepatic failure.

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I will not go into the details of the comparative numbers, but I will broadly summarize the epidemiology conclusions here. That is, the calculated reporting rates for all three drugs were comparable for the serious cardiac events and seizures. In other words, none of the drugs stood out for either of these two events. Furthermore,

these reporting rates were below the background rate for all three drugs and for all events, including the hepatotoxicity with loratadine.

However, due to the limitations of the data in these analyses, a safety problem for one or more of these drugs cannot be excluded, but the data are also reassuring in terms of there not being a clear signal either.

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So, let me sum up the overall clinical and regulatory conclusions from the FDA's perspective. Overall, loratadine, fexofenadine and cetirizine have extensive favorable marketing histories and safety profiles. The Food, Drug and Cosmetic Act under the Durham-Humphrey Amendment sets criteria for when a drug should be Rx only versus when it should be available over-the-counter. The U.S. market has over-the-counter antihistamines available to treat systems of allergic rhinitis.

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The WellPoint petition requests FDA to initiate a switch of three prescription antihistamines to OTC status, and action that actually the federal regulations allow for, that a petitioner can come to the Commissioner and ask for

such removal from Rx status.

Available data for these drugs supports them being effective for allergic rhinitis and we are not necessarily seeking advice on that today. There are certainly some low frequency safety signals that arise from our review of the safety database, however, using a weight of evidence approach, including consideration of all the preclinical or animal studies, the in vitro testing, the clinical testing under controlled conditions and the adverse event database, we feel that these three products have a favorable safety profile.

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Therefore, the advice we are seeking from the combined committees today is given the current OTC status of certain antihistamines for the treatment of allergic rhinitis and the safety information discussed today, as well as all information that comes from other sources related to safety, should each individual drug be available OTC? Again, we are asking to separately consider these. This is not an all or none package.

If your recommendation is that any one of these should not, what other safety studies or

other information would be required or recommended for us to seek prior to such a switch? If, in fact, your recommendation is yes for any or all of these moieties, we would ask what modifications to the existing OTC antihistamine labeling would you recommend? Thank you.

Questions from the Committee to the FDA

DR. BRASS: Thank you. We have a few minutes which we will spend discussing the FDA presentation but, again, I would remind everybody that there will be time later in the afternoon for questions as well. Dr. Cantilena?

DR. CANTILENA: Yes, Dr. Meyer, can I ask you did your evaluation of the cardiac safety of Claritin include a publication just this year, I believe it was a couple of months ago, in Clinical Pharmacology and Therapeutics, which was a Georgetown study looking at a drug-drug interaction with Claritin and a 3A4 inhibitor that showed not only a pharmacokinetic action but also significant increase in the QTc interval? If you have looked at that, would you say that that change in the QTc was not clinically significant?

DR. MEYER: We are aware of that study and did look at the study to the extent we can.

Obviously, it is a publication that we did not primarily review, but I would say that there are a couple of points we would make about that study. Its original intent was, in fact, to use loratadine as a negative control for the other -- I believe it was an antidepressant that was in the study. In fact, the correction method used for the heart rate in the study was -- I think it is hard to know what that might have done. They used Bazett's correction for lower heart rates and Fredericia's for higher heart rates. They kind of split it in the middle.

I think the upshot of it is that we are not sure we can make sense of all the data, particularly in the light of the other data that are available to us and everything else we know. So I think, by and large, we note it but I would say that we, at this point, have some concerns about whether that is a meaningful study for us.

DR. CANTILENA: So, after you have a chance to look at it, if you conclude the study was done correctly, is that going to sort of change your conclusion in terms of the cardiac safety of Claritin?

DR. MEYER: Again, probably not. I mean,

it would be important for us to take that under consideration I think, but we are talking about a weight of evidence approach here, and we have other data that this stands in contradistinction to. So, I think we wouldn't necessarily just discount something offhand but I think that we need to take a weight of evidence approach.

DR. BRASS: Dr. Niederman?

DR. NIEDERMAN: When you consider these drugs going over-the-counter there is certainly the potential that people will be taking them under less supervision for a longer duration and maybe for non-indicated situations. Are you able to tell in your review of the data of side effects whether or not side effects were more or less likely to occur, or how often they occurred in patients who were taking it for a non-appropriate indication or for maybe a more prolonged duration of time than would have been recommended?

DR. MEYER: I am sorry that I missed the initial part of your question but I assume you are asking about the adverse event reporting data.

DR. NIEDERMAN: I am asking if they become over-the-counter and there would be less physician supervision, do we know from the adverse events

whether they are more likely to occur, or occurring in people without indication or taking it for a longer time than maybe is recommended or would be recommended under supervision.

DR. MEYER: Yes, I would certainly invite comments from OPMDRA colleagues who also did the primary review of these reports, but I would say that it would be very difficult to actually do such an analysis based on the reports. You commonly don't know the duration of treatment. You don't know the circumstances of its use. Other than, say, a clear report of intentional overdosing over time, that sort of thing, it would be very hard to actually do that sort of analysis.

DR. BRASS: Dr. D'Agostino?

DR. D'AGOSTINO: Just in terms of trying to inform me about more safety data of we think it is necessary and what types of studies would be needed, I want to go back to your slide that said neither an in-use study nor a labeling comprehension study are necessary for the OTC switch proposed. In some of the earlier presentations and some of the readings there were distinctions being made between the first generation and the second generation in terms of

the short-term use versus chronic use, in terms of the simple symptom relief with the first generation and complex conditions with the second, and then things like the common cold where the first generation effectively deal with them and the second generation don't. So, I assume that the statement you made about the in-use study and the label comprehension come because of the first generation data, yet, are we not to take seriously statements like chronic use and short-term use, and simple relief versus complex conditions?

DR. MEYER: I wouldn't want to characterize whether you should take something seriously or not. What I would point out, however, is that the indication in the prescription labeling is not very much different from what it would be in the OTC labeling, and the particular sponsor that discussed this -- that drug, Claritin, does not have an indication for complicated allergic rhinitis; it has an indication for seasonal allergic rhinitis.

So, I think, you know, it is sort of an interesting assertion that I didn't see data for, but also it sort of really does not speak to the indication that loratadine currently has.

DR. D'AGOSTINO: So, these distinctions are sort of new on the table between the first and second generation uses.

DR. MEYER: I would say that they are new on the table and, again, I am not aware of data to establish that that is the case. If the OTC antihistamines, both under the monograph and otherwise marketed under NDAs, are used in these kinds of limited, sort of more benign patients, that perhaps speaks to the success of the OTC drug labeling and I don't know why we should suppose that we would lack that success if that same labeling were used for loratadine, for cetirizine or for fexofenadine.

DR. D'AGOSTINO: Thank you.

DR. BRASS: Dr. Dykewicz?

DR. DYKEWICZ: I was hoping you could elaborate a bit more on the pediatric safety studies that are ongoing with fexofenadine. When do you anticipate that those would be completed? Also, has the agency essentially completed its studies about pediatric use of cetirizine relative to safety?

DR. MEYER: Well, the agency does not strictly do the studies. It is within the purview

of the sponsor. We do have a current pediatric initiative to get pediatric data, partly under written request. I would point out with regard to what the sponsor said about the ongoing studies that I think, by and large, the pediatric written requests include asking for data for populations that are in extreme often of labeling -- I am talking in general now -- because of known use in those populations. So, I think in terms of doing a reasonable safety evaluation in the pediatric population you would consider doing things like cardiograms and other special testing, where you might not have questions in adults about the effects, just because you are entering into a quite young population often.

I am not directly answering your question because some of it I can't directly address other than what the sponsor said. But, again, just to sort of qualify what the sponsor did say, yes, they stated that we had asked for some electrocardiograms in children but I think that that would not be a unique request for such a study.

DR. BRASS: Dr. Roden?

DR. RODEN: I have many questions but for

this presentation I have just a couple of points of clarification. First of all, can you clarify for me what the current approved labeling is for these three compounds? I know that they are in the briefing book but at least one of them is too small for my terrible eyes --

[Laughter]

-- so, the question is whether all the discussion we have heard about long-term management of the allergic patient falls in the purview of the currently approved label.

DR. MEYER: That is a good question, and I think you could get into some debate about seasonal allergic rhinitis because in some patients the season can be quite long. For instance, grass allergy can be more than a simple two weeks. Tree allergy is often shorter.

DR. RODEN: Like twelve months?

DR. MEYER: No. But in terms of perennial allergic rhinitis which clearly can be a much more chronic condition, if I recall correctly, it is only cetirizine or Zyrtec that currently carries that specifically in its labeling. I actually think their direct consumer advertising reflects that.

DR. RODEN: Another issue with respect to safety, one of the things that was a signal in the early terfenadine experience was the overdoses because that clearly gave a cardiac signal. Is there overdose experience with these three compounds of any type? Along the same lines, can you compare again or review again what the incidence of cardiac arrhythmias was in the terfenadine experience, say, between 1985 and 1989 when people weren't sort of tuned into this possibility compared to the kind of rates that you quoted for us for the other three drugs?

DR. MEYER: The last question I think is very tough because you do have temporal trends. In fact, we are in an era now where people are somewhat tuned into these potential effects. For instance, if one were to give Allegra and see a cardiac event I think a physician might say, well, I know this is related to terfenadine and I really should report this. So, we have looked at those sorts of data and don't find any signal for concern, but it is very tough to do with the data that are available to us.

I am blanking on your first question. Oh, overdose. We do have some overdose experience with

each of the drugs. I don't know whether the folks from OPMDRA would like to say anything about it. There was one particular case that I believe occurred with loratadine where there were very, very high doses taken and there was some evidence of QT effects but that was also in the setting of other drugs of abuse in that patient, and it was not clearly a case where the overdose itself caused the cardiac effects.

DR. RODEN: Were there arrhythmias though?

DR. MEYER: I believe in that case there were. Let one of my colleagues from the Office of Post-Marketing Drug Assessment come up.

DR. WEAVER: Yes, I will just go through the fairly large overdoses that we had. For loratadine we have a case of a female of unknown age took 15-20 tablets of Claritin, but it was the D formulation, and had tachycardia.

A 3-year old boy took 45 mg and became drowsy. A 17-year old took a full bottle of Claritin, along with some diet pills, and experienced respiratory insufficiency requiring intubation, with tachycardia oliguria and somnolence.

An 18-year old took 300 mg of Claritin,

had tachycardia to 150 beats per minute, respiratory alkalosis and a normal QT in that case. That was the case that was published in the literature.

A 2-year old child took 120-150 mg, had minimal, unspecified tachycardia and nervousness. A 2-year old boy took 100-150 mg, had tachycardia to 150 beats per minute and a QTc of 413 milliseconds.

DR. RODEN: Aside from tachycardia, do you have anything that says arrhythmia because those are all not arrhythmias?

DR. WEAVER: We had a 53-year old female with no prior cardiac history who took actually only 20 mg a day for 2 weeks and had acute ventricular tachycardia requiring electrical defibrillation. That is it for the experience for loratadine.

DR. MEYER: I would also point out again that we do have within the NDA database high dose studies, basically looking specifically at the cardiac safety.

Actually, I would like the opportunity, if I could, just very quickly to ask Dr. Roden for any views you might have on the study that I was

initially asked about the possible QT effects.

DR. RODEN: You mean this one? The reason I am sort of trying to dredge the large experience is that this is a relatively small study. There are a couple of little things about it that I find peculiar in the sense that they don't have much of a change in plasma concentrations either of parent drug or metabolite, yet, cite a readily detectable QT signal using this peculiar rate correction that you alluded to.

So, I am not sure what to make of it one way or the other, and I am much more interested, given the very large experience with these drugs that has accumulated to date, whether there is a safety signal when they are used. In the end it doesn't much matter whether they are HERG blockers or whether they prolong the QT five milliseconds under some experimental condition, if you have used it in thousands and thousand of patients and are attuned to the possibility of an arrhythmia and don't see much. That is probably more meaningful. So, I am not sure how to be reassured about these data. I am not sure how to interpret them.

DR. MEYER: I guess the one other point I want to make then in regard to your question is

that there are also limitations to our database in terms of the specific arrhythmia that we are worried about, the Torsades. It is not always captured in the setting where you would expect it to be, and since it is a relatively less common tachyrhythmia it can get overwhelmed in any signals where you are trying to assess relative reports --

DR. RODEN: Although the overdose experience with terfenadine -- you know, it is the toxicity of terfenadine. With overdose Torsade is what happens. So, if there are overdoses with all these other drugs and that is not what happens, I find that reassuring.

DR. MEYER: Right, and in general I think that would be our answer, that we are not really seeing a signal coming out of the overdose experience we have.

DR. BRASS: Dr. Clapp?

DR. CLAPP: Dr. Meyer, I would like clarity on the FDA perspective on the significance of the AERS report from March, 2001 regarding Zyrtec and 39 percent having CNS or peripheral nervous system or psychiatric disorders, and complaints of that. Specifically, the interesting finding that I noted in reading that report was

that there were 16 attempted suicides of deaths or 4 that didn't have any co-morbidities and were left unexplained. In reading this, I am wondering about the significance of this considering the recent experience with Accutane and labeling Accutane, which is a very highly controlled substance for physician prescription use only, and what body of evidence was needed to relabel Accutane, and then comparing it to the consideration of making Zyrtec over-the-counter in light of these reports.

DR. MEYER: Again, I actually can't speak to the specifics of Accutane but I would again point out that you are talking about often a fairly young, healthy population that are given antihistamines, and that there are certain background rates for these kinds of events. Although these things are cited in our review, specifically the suicide did not stand out as any kind of signal that we felt should otherwise be strongly considered in terms of the prescription marketing or the OTC marketing of these.

I would say as far as the overall CNS adverse event profile of Zyrtec, it is obvious or apparent from the look at the top adverse event reports in the NDA that there are perhaps more CNS

effects or penetration perhaps with cetirizine than the other two agents in questions today. Not to directly compare but I guess we can't help it to some extent, but if you cut across through the data for the others, there are actually fairly frequent side effects for the others as well. It stood out a little bit more with the cetirizine database but it did not seem to be unique, other than the fact that the reports were a bit more prominent in number.

DR. BRASS: At this point, because of the hour, we are going to break for lunch. For the committee members who signed up for lunch, they will be served in the restaurant. There is an area that has been reserved for the panel members.

I would also like to remind the panel that during lunch you are not to discuss the issues before the committee today or interact with petitioners or sponsors. We will reconvene promptly at one o'clock according to my watch.

[Whereupon, at 12:15 p.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

AFTERNOON PROCEEDINGS

Open Public Hearing

Professional Associations

DR. BRASS: The afternoon begins with a continuation of the open public hearing. Again, I would request from the presenters that they begin with identification and addressing the conflict of interest and sponsorship issues, and I thank them in advance for keeping to their five-minute time schedule. Our first speaker will be Dr. Lanier.

DR. LANIER: I would like to thank the panel very much for the opportunity to be a part of this historic event. My name is Dr. Bob Lanier. I am a pediatrician by primary training, and by secondary training a specialist in the management of individuals affected with the genetic aberration of allergy, asthma and related entities.

I would like to address the twelve scheduled conflicts although, to frustrate the counter, I will do them not necessarily in the order presented. In the 30-plus years since my graduation I confess to contributing to the public good by performing double-blind, placebo-controlled FDA-sanctioned, randomized clinical trials of both first- and second-generation antihistamines. I

have also consulted in that function from time to time with the three companies.

With that in mind, you might classify me as having a conflict, but I would remind the panel that familiarity occasionally breeds contempt. I own now, nor have I ever owned any stock in any of these companies, nor have my expenses in any way directly or indirectly been covered by these companies. I presented study data to groups of doctors at academic meetings and quasi-academic social meetings for which I received a fee.

I also confess, having been a senior vice president of a major health plan for nine years, charged with communicating managed care philosophy to the community and the familiarity and contempt reference also applies here.

I represent the 4000 allergists from two major national organizations, the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. Our organizations receive both unrestricted and educational grants, advertising revenues from vendors for products for allergic and asthmatic patients, including the three pharmaceutical companies. Our organization advocates for our

patients, the great majority of which will be affected by the eventual decision being discussed here today.

The American College and the American Academy take neither an HMO pro response or an anti pharmaceutical response, but we do oppose the switch of these antihistamines from prescription to OTC at this very pivotal time in which the medical system is in transition. It has been fifty years since Durham and Humphrey put together the Bill that brought us here today -- fifty years. At the time that this was presented, less than ten percent of people had insurance, had any sort of healthcare assistance at all; ninety percent did not. Now we find the paradigm is completely reversed. Ninety percent of people have some form of assistance and ten percent do not. Therefore, some of the basic tenets of the spirit of the Humphrey-Durham act need to be re-looked at.

I had the joy of reading the congressional testimony in the Federal Register about the development of those bills in the '40s and the early '50s when it was finally advanced, and I would urge you to do the same thing. You would be inspired by it.

Now, whether the request for testimony today has been restricted to considerations of safety, safety is the culmination of many factors and any attempt to focus on any one factor may do the public harm. I would like to discuss safety on both an individual and a mass platform. The American College and American Academy say, if approved, the placement of these compounds on the OTC market will result in reduced availability of these valuable medications to our patients. The cost of these drugs will likely make them unavailable to patients who received them through insurance covered formularies. OTC availability will eliminate the physician from the care process of patients taking antihistamines. Overuse or misuse of this class of drugs for disorders which have no proven efficacy will increase health cost.

Allergies are not necessarily a self-diagnosable problem. We have a problem with the stance that has been presented here today. Although 20-30 percent of the population are allergic, we know by surveys that 75-80 percent of people feel like they are allergic. Everybody has got a little allergic to something and, because of that, this disease is trivialized. This is a

chronic problem and it lasts a long time. By placing these agents in an OTC status this trivialization will continue to occur. Reduced availability or utilization of these drugs without physician evaluation may mask or delay symptoms of larger diseases.

We are concerned because our organizations are dealing with children in many cases. It is the conclusion of our members that these three drugs are safe in the individual adult. We are not yet convinced of that in children. Children are not just scaled down adults. They have different metabolism. We are concerned they will be used in children in high doses since they are being used in low doses now by prescription. We need the surveillance system that only goes with prescription medications.

We are also concerned from a safety standpoint when overnight, with a stroke of a pen, millions of working poor will be denied access to non-sedating antihistamines by virtue of an OTC status. Poor patients can't afford the existing OTC medications. What happens when you have a new one? Can anyone rationally say these will cost the same or less than what we have there now?

Remember, we are talking about a chronic disease. We are talking about a problem that continues for a long time.

So, who bears the responsibility for driving accidents? From a mass standpoint because of costs, this is unfair and unsafe for poor people. For indigent people it is a disaster. I have in my own small practice over 200 families that are on compassionate medicine programs provided, among others, by the three companies here involved. There is no source of compassionate OTC medications or generic medications at all.

What we are witnessing here is a clash of titans. HMO plans are infuriated by DTC advertising and pharmaceutical companies have not yet communicated a rational picture to describe the enormous inequities of cost from one company to another. The American College and American Academy challenge the petitioners and the industry and the regulating bodies to negotiate a settlement which is beneficial to allergic people. The American College and American Academy support what is good for people but we have particular interest in the poor and the indigent who, we feel, will be harmed by this action. It would certainly be interesting

to know what Hubert Humphrey would say about these hearings but, you know, I don't think he would support it. Thank you.

DR. BRASS: Thank you. Our next speaker is Dr. Kaliner.

DR. KALINER: Panel members, I am Mike Kaliner. I am the Medical Director for the Institute for Asthma and Allergy here, in Washington, and former Chief of Allergy at the NIH, former President of the Academy of Allergy, and currently Vice President of the World Allergy Organization.

I have some conflicts that I would like to mention. I consulted with, advised and lectured for all three companies, in addition the companies that make OTC antihistamines currently available. My Institute does research with every company that makes allergy and asthma products. I am a preferred provider, at least I was until today, with the local Blue Cross/Blue Shield --

[Laughter]

-- and by their reckoning, I am their number one provider in the Washington, D.C. area. At least I was.

Panel members, you are being asked to

consider an extremely complex issue of whether to recommend that safe and effective medications, used for the treatment of allergic rhinitis, be switched to OTC status against the wishes or without the compliance of the manufacturers. This issue has been precipitated by desires of WellPoint Insurance Company to switch the cost of providing these medications from their pocket to the pockets of their members. I am not going to address the cost of such a switch and who will bear these costs, as others have, and will continue to do so.

I want to take a different slant. I want to address the position that this petition and the FDA's decision to address it have placed you. I have been close to being on your panel on a number of occasions.

Over the years, the legislatively mandated patent protection laws have allowed pharmaceutical managements a period of time to market their successful products in the Rx only market in order to pay for the research and development of new products. That revenue stream from products in the Rx market differs from that in the OTC market, and many ethical pharmaceutical companies are not equipped to market in the OTC environment, and some

of the companies we are talking about today cannot do that kind of marketing. Thus, forcing an OTC switch might materially affect the revenue of these companies.

Moreover, there is another predictable outcome from forcing an OTC switch which really concerns me. Let me ask if a company develops a safe and effective product in an area where reasonable diagnosis can be made by an educated patient, does that mean it should automatically go OTC? Does that ruling apply to all products used to treat this disease? At what point will you determine that a product should be forced OTC? Will you automatically review all products, including the dozens of safe and effective sedating antihistamines, decongestants, combination tablets, mucoevacuents and anticholinergic products currently sold for the treatment of allergic rhinitis by prescription only, or will you limit your ruling today to just the top few products?

How will you determine when and by whom these products should be reviewed? What about new applications and new approvals? Will you give them an exclusive occupancy of the Rx only market by excluding the other products that you shifted to

OTC? What about topical nasal corticosteroids?

I believe you have to be even-handed in these deliberations and decisions, and anything you decide has to apply to the whole field and not just selected products.

I also ask you to look at this from the industry's perspective. If a company anticipated that safe and effective products in an area like allergy will face limited time, protected time in the prescription only marketplace, then why would companies continue to develop such products? I believe that they would stop development of allergy products immediately and there would be no future products developed in this area until there was additional legislative protection.

In fact, I have concerns about the panel deciding this issue, which I think infringes on companies' rights, and this is more a legislative than a regulatory area. Notwithstanding, forcing companies to move their prescription products to OTC against their will, will establish a powerful precedent which could have enormous effects on the future of the development of all prescription products. It is one thing when a company petitions you to allow a safe and effective product at

appropriate doses to go OTC, but it is quite another for you to force them to abort the revenue stream of an effective product prematurely.

In my opinion, this ruling will cause enormous losses in their revenue. If a U.S. government ruling costs these companies money, is there compensation available? Would that compensation come from the FDA budget?

In summary, allow me to ask are you prepared to create havoc in the patent protection of pharmaceutical products? Are you able to determine which products come under scrutiny for OTC switch? When should these products be reviewed and by whom? Are you prepared to stop new product development in fields like allergy, and are you prepared to compensate these companies for the loss of revenue?

If I were in your seat, I would avoid this issue entirely and recluse myself from any decision. In my opinion, this is an inappropriate use of your time and forces you into a decision-making process which might have huge consequences, far beyond the regulatory roles for which you all volunteered.

In my opinion, the petition by WellPoint

is flawed for many reasons but the most critical aspect of this issue is the consequences of this ruling and its effect on new drug development. As an allergist, I look to these companies to develop new and more effective products for my patients. If you continue this review and rule in favor of WellPoint you might just have stopped new product development in allergy forever. I hope that you take my advice, reject the petition and avoid making any ruling on this issue. Thank you.

DR. BRASS: Thank you. Our next speaker is Ms Nancy Sander.

Patient Advocacy

MS. SANDER: Thank you. It is a great pleasure to be here. As President of the Allergy and Asthma Network Mothers of Asthmatics, a non-profit education and advocacy organization dedicated to eliminating death due to asthma and to allergies, thank you for this opportunity to oppose OTC status for non-sedating antihistamines.

Since 1985, AANMA has enjoyed excellent working relationships, and received educational and unrestricted grants from numerous research-based pharmaceutical and device manufacturers. During 2001, we did receive contributions from

manufacturers of medications in question, in combination totaling less than 50,000 dollars.

Neither AANMA nor myself own any stock or enjoy any financial interest in companies represented in this issue. AANMA pays my salary and I have received and accepted no offers for expenses or opinions related to this subject. I stand before you representing the best interests of more than fifty million consumers affected by allergies and asthma. I also stand before you as an employer with the best health insurance that she could find for her employees, which is Blue Cross/Blue Shield CareFirst. I also am a person who enjoys excellent care through this program.

AANMA opposes OTC status for non-sedating antihistamines. Asthma and allergies are serious, potentially life-threatening conditions, as previous speakers have said. However, the average consumer does not have the knowledge or possess the necessary skills to safely self-diagnose and treat allergy symptoms without medical guidance. At best, their efforts are experimental, and you don't have to go far to find evidence for this. Just go to your local grocery store and stand in the cold and cough aisles of the grocery store and you will

witness consumers seeking medical advice from stocking clerks as to which medications they should take home.

But when allergy symptoms drive the patient to the doctor instead of the grocery store, the physician examines the patient, takes a medical history and, if needed, conducts diagnostic tests, taking all this information into consideration for treatment strategies developed for that person, and they may even get to spend some time with a nurse educator.

Their treatment plan will allow them to take the medication that provides the greatest results with minimal or no medication side effects. That medication is not necessarily always a non-sedating antihistamine. In fact, the patient may receive a prescription for one or more topical nasal corticosteroid sprays to reduce inflammation and congestion in the nose. The physician may also prescribe a simple recipe for a saline nasal wash, a medication-free and inexpensive way of removing the offending allergens from the nasal passages. Furthermore, it is at this appointment where patients learn, like me, how to prevent episodes of allergies from returning. That means I am at work

and my kids are at school.

If only managing asthma and allergies were as simple as popping sugar-coated, non-sedating antihistamines available OTC, but it is not. Chronic allergies take many forms. Some are more subtle than others. But in all cases consumer ignorance is not bliss. Tell me how even the most intelligent adult differentiates between a sinus infection and allergy, or a cold and asthma, or a cough due to allergy, asthma, sinusitis or the flu. And, if we can't accurately self-diagnose, where do we begin to self-medicate?

As a patient advocate and a mom of four great kids, three of whom have allergies and three of whom have asthma, I am concerned that the people whom I trust to understand these issues, my health insurers, are seeking OTC status for chemically distinct non-sedating antihistamines as if they were candy. Is this trust ill placed?

Health insurers say non-sedating antihistamines are safe, and I agree, but only when used as prescribed by a physician. While it is true that in Third World countries I can purchase just about any asthma, allergy, high blood pressure or other kind of medication over-the-counter, those